UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,338	03/15/2005	Jose Cosme	BJS-620-347	6158

23117 7590 09/06/2007
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
KIM, ALEXANDER D	
ART UNIT	**PAPER NUMBER**
1656	

MAIL DATE	DELIVERY MODE
09/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,338	COSME ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10,11,13 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10,11,13 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/2007,03/29/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office actions, a non-Final rejection (mailed on 02/16/2007), Applicants filed a response and amendment received on 06/18/2007. Said amendment cancelled Claims 14-20, amended Claims 1-2, 4, 10, 11 and 13; added new Claims 21-23. Thus, Claims 1-13 and 21-23 are pending in the instant Office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed on 06/18/2007 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

The information disclosure statement filed 03/29/2007 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Withdrawn-Compliance with Sequence Rules

3. The previous non-compliance with Sequence Rules is withdrawn by the virtue of Applicant's amendment.

Withdrawn-Objections to the Specification

4. The previous objection to the specification because the title is not descriptive of the claims is withdrawn by the virtue of Applicant's amendment.

5. The previous objection to the specification for a typographical error in the Table 1, page 30, is withdrawn by the virtue of Applicant's amendment.

Maintained-Objections to the Specification

6. The previous objection to the Abstract is maintained. The applicants argue the amended Abstract overcomes the instant objections. However, the name of source species (human) is not included; thus, the Abstract does not completely describe the disclosed subject matter (see M.P.E.P. § 608.01(b)).

Withdrawn-Claim Objections

7. The previous objection of Claim 18 is withdrawn by virtue of canceling Claim 18.

New-Claim Objections

8. Claim 13 is objected to because of the following informalities: Claim 13 recites "further comprising crystallizing". It should be ---further comprises crystallizing---. Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

9. The previous rejection of Claims 1-13 and 18 under of 35 U.S.C. 112, second paragraph, is withdrawn by the virtue of Applicant's amendment.

10. The previous rejection of Claims 4-5 under of 35 U.S.C. 112, second paragraph, is withdrawn by the virtue of Applicant's amendment.

11. The previous rejection of Claims 10-12 under of 35 U.S.C. 112, second paragraph, is withdrawn by the virtue of Applicant's amendment.

Maintained-Claim Rejections - 35 USC § 112

12. The previous rejection of Claims 4-5 under of 35 U.S.C. 112, second paragraph, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue one of ordinary skill in the art will appreciate the metes and bounds of the claimed invention in view of specification and general level of skill in the art, wherein the specification teaches that rapid desalting is a process of using a desalting column with a "relatively high flow rate such that the desalting occurs in less than about 30 min, e.g. less than about 10 min" (see top of page 11) whereas a more common dialysis takes many hours or days.

However, the method step of using a gel filtration column which takes less than 30 min. or 10 min. is not a claim limitation. Because the "Limitations appearing in the specification but not recited in the claims should not be read into the claim" (see MPEP 2106[R-5] II), examiner suggest adding such limitation into the claim for consideration. It is noted the Applicants seem to acknowledge the instant method is relative based on the recitation of "relatively high flow" in the Remarks as shown above.

13. The previous rejection of Claims 10-11 under 35 U.S.C. § 112, first paragraph,

written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the applicants were in possession of the claimed invention at the time of the application was filed and the Examiner failed to properly characterize the state of the art and knowledge of the biology of P450s with the teachings of the present specification as well as the generally advanced level of skill in the art. Applicants argue that Szklarz's (1991) alignment in Figure 1, p. 266, and in view of Kempf (1995) describe the genus of N-terminal membrane inserting element. Applicants also argue examples by the specification and the prior art describes the claimed genus of methods comprising the purification of a protein lacking known genetic sequences, wherein the genetic sequences are described by Wachenfelt et al. (1997, expressing a rabbit P450 2C3 and 2C5 isoform in E. coli with deletion of 3-21 at the end of N-terminus), Gillam et al. (1995, expressing the human N-truncated forms of cytochrome P450 2D6 without the N-terminal hydrophobic region), Larson et al. (1991, expressing rabbit cytochrome P450 2E1 without 3-29 n-terminal) and Saraga et al. (1993, expressing bovine P450 without residues 2-17). Applicants argue the truncation of proteins at this region was commonly practiced.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Thus, as previously noted, the instant specification and the prior art failed to describe a widely varying claimed

genus method sufficiently to represent a genus method of purifying P450 having deletion of genus membrane inserting element, which is comprised of unlimited structure having unlimited amino acid residues. The prior art above seem to indicate any residues rich in hydrophobic residues are encompassed in a N-terminal membrane inserting element. Furthermore, the Applicants acknowledge the removal of predicted membrane inserting element in a P450 does not always remove membrane association of P450 by the disclosure Larson et al. (1991) who disclose the P450 without the membrane inserting element also fractionated with a "predominantly in the membrane fraction" (see middle of page 14, Remarks), which does not supports the structure and function of claimed N-terminal membrane inserting elements. However, the disclosure of deleted sequence (i.e. N-terminal membrane inserting element) by the prior arts and by the instant specification do not describe any structure and functional relationship to predict a structure of other member of the species within the full scope of claimed genus. Thus, for the reasons above, the instant rejection is maintained.

14. The previous rejection of Claim 13 under 35 U.S.C. 112, first paragraph, written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue "the Examiner's objection does not extend to these species" of P450 2C9, P450 2C19, P450 2C19-1B, P450 2D6 or P450 3A4. Applicants argue the teaching of the instant specification overcome the rejection because the instant specification provide about 140 specific different crystallization conditions for P450 2C9,

P450 2C19, P450 2C19-1B, P450 2D6 or P450 3A4, which all resulted in formation of P450 crystals. Applicants also argue the instant claims do not require "any specific diffraction quality" in view of lacking such limitations in the Claim 13.

It is noted that this is not an objection as recited in the Remarks (page 16, line 1). It is rejection under 35 U.S.C. 112, first paragraph. The "genus of method crystallizing any P450, as disclosed in Claims cannot be adequately described by the disclosure of the instant specification. The species of instant case do not correlate structure and function from species to genus. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, any method of crystallization encompassed by the breadth of the claims is not adequately described by the representative species of methods of crystallization disclosed in the specification." (see bottom of page 10, the previous Non-Final Office Action). The disclosure of about 140 crystallization condition by the instant specification seems enough to describe the genus method sufficiently, but the claimed genus of P450 encompassed by the method is so large, the 140 disclosed crystallization condition is not sufficient to describe the function of crystallization and structure of buffer relationship. For example, there are about 50 sequenced isoforms of P450 from a human alone as disclosed in the instant specification page 2, lines 14-15. Thus, the disclosed species by the instant specification do not describe the genus of method comprising a genus method step of crystallizing even wider genus of P450 encompassed by the breadth of the claims in order for one skilled in the art to crystallize (or possess) the full scope of the claimed

method comprising a very widely varying P450 genus. Examiner acknowledges the absence of limitation regarding the diffraction quality in the claimed method. For the reasons above, the instant rejection is maintained.

15. The previous rejection of Claims 10-11 under 35 U.S.C. 112, first paragraph, scope of enablement, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the full scope of claimed inventions are enabled at the time of the application was filed and the Examiner failed to properly characterize the state of the art and knowledge of the biology of P450s with the teachings of the present specification as well as the generally advanced level of skill in the art. Applicants argue that Szklarz's (1991) alignment in Figure 1, p. 266, and in view of Kempf (1995) describe the genus of N-terminal membrane inserting element. Applicants also argue examples by the specification and prior arts describe claimed genus method comprising the purification of protein lacking known genetic sequences, wherein the genetic sequences are described by Wachenfelt et al. (1997, expressing a rabbit P450 2C3 and 2C5 isoform in E. coli with deletion of 3-21 at the end of N-terminus), Gillam et al. (1995, expressing the human N-truncated forms of cytochrome P450 2D6 without the N-terminal hydrophobic region), Larson et al. (1991, expressing rabbit cytochrome P450 2E1 without 3-29 n-terminal) and Saraga et al. (1993, expressing bovine P450 without residues 2-17). Applicants argue the truncation of proteins at this region was commonly practiced.

However, as noted in the previous office action, the breadth of claims encompasses a genus method of purifying any P450 with deletion in N-terminal membrane inserting element (which has unlimited structure). The applicants failed to disclose direction or guidance regarding purification of widely varying a P450, wherein the P450 lacks very widely varying N-terminal membrane inserting element. Furthermore, the Applicants acknowledge the removal of predicted membrane inserting element in a P450 does not always remove membrane association of P450 by the disclosure of Larson et al. (1991) who disclose the P450 without the membrane inserting element also fractionated with a "predominantly in the membrane fraction" (see middle of page 14, Remarks). Thus, many examples by the instant specification and prior arts fails to describe how to make and use the full scope of claimed genus method sufficiently for purifying any P450 which lacks any N-terminal membrane inserting element. Because the claimed genus method comprises very widely varying P450, it is unpredictable to determine how much of a N-terminal should be removed for one skilled in the art to make a membrane binding P450 to become soluble. Thus, the claimed method is unpredictable and undue experimentation is required for one skilled in the art as noted in the previous office action (bottom of page 13). For the reasons above, the instant rejection is maintained.

16. The previous rejection of Claim 13 under 35 U.S.C. 112, first paragraph, scope of enablement, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the teaching of the instant specification overcome the instant rejection because the instant specification provide about 140 specific different crystallization conditions for P450 2C9, P450 2C19, P450 2C19-1B, P450 2D6 or P450 3A4, which all resulted in formation of P450 crystals. Applicants also argue the instant claims do not require "any specific diffraction quality" in view of lacking such limitations in the Claim 13.

However, as noted in the previous office action, Claims 13 and 18 are so broad as to encompass a method that comprises making any cytochrome P450 protein crystals in any crystallization condition and/or determining crystal structure of any cytochrome P450. "The methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was at least challenging to a skilled artisan" (see top of page 15 in the previous Office Action). The instant specification disclosing about 150 condition (crystallizing only a species of P450) and few examples by the prior art cannot predict the overly broad scope of the claims; thus, lacking the guidance and sufficient working examples; makes the full scope of claimed method unpredictable; requiring an undue experimentation for one skilled in the art to make and use the full scope of claimed method. Examiner acknowledges the absence of limitation regarding the diffraction quality in the claimed method. However, it is unclear how the Applicants would use the crystal without the diffraction quality even if any crystal is made. For the reasons above, the instant rejection is maintained.

Maintained-Claim Rejections - 35 USC § 102

17. Claims 1-4, 6-8, 10 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by the reference of Kempf et al. (1995, Archives of Biochemistry and Biophysics, vol. 321, p. 277-288, **as cited in the IDS**).

The rejection was stated in the previous office action as it applied to previous Claims 1-4, 6-8 and 10. In response to this rejection, applicants have amended Claims 1-2, 4, 10, 11 and 13; added new Claims 21-23; and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered and are deemed not persuasive.

Applicants argue the Kempf et al. used acidic form of HEPES based on the Kempf et al. reciting "N-[2-hydroxyethyl]-N'-[2-ethanesulfonic acid]" not sodium salt form of HEPES supported by the availability of both acidic form as well as sodium salt form of HEPES from the Sigma chemical supply company (copy of catalog attached by Applicants). However, as Applicants also acknowledged, it is the explanation of the abbreviated term "Hepes" and does not provide the evidence that Kempf et al. used the acidic form of HEPES. Thus, Applicants' arguement that the AD buffer of Kempf et al. having 150 mM NaCl with 50 mM Hepes (if acidic form is used) does not have a total salt concentration of 200 mM is not persuasive.

Further, given the broad and reasonable scope of the instant claims with open-ended term "comprises", the method steps of Kempf et al. continues to meet all limitations of Claims 1-4, 6-8, 10 and 21-23 and the reasons are described below in detail. It is noted that instant amended limitation of "about 500 mM" for salt

concentration in Claim 2 was not required to meet in the previous Office Action. However, this limitation is also met because of the broad scope of the instant method steps encompassing method steps in a different stages of method taught by Kempf et al.

Claim 1 is drawn to a method for the purification of a cytochrome P450 comprising: (a) expressing in a host cell, (b) recovering the cell from the culture and suspending in a salt buffer having a salt concentration of 200 to 1000 mM and a conductivity of 12 to 110 mS/cm, (c) lysing the cell and removing cell debris, (d) adding a detergent to the lysate and (e) recovering the P450 from the lysate, wherein the P450 is not a human 2C9 P450 with Pro220 substitution when the salt concentration is 200 to 1000 mM. Claims 2-4, 6-8, 10 and 21-23 have additional limitations as disclosed in instant claims.

Kempf et al. teach a method for the purification of His-tagged "N-terminal truncated human cytochrome P450 2D6" ($[His]_6$-**CYP2D6**-Δ25, see bottom of left column, p. 278) and the $[His]_6$-CYP2D6-Δ25 protein as shown in SDS-PAGE gel Figure 3, p. 282, wherein the "N-terminus 25 amino acids --- serve as a membrane anchor" (see Abstract). Kempf et al. teach the method steps comprising: "transformation into E. coli JM109" with "expression plasmid $[His]_6$-CYP2D6-Δ25" (see top of left column, p. 279) and culturing the transformed E. coli as disclosed in "Expression of truncated human P450 2D6" (see middle of left column, p. 279); which meet the limitation of Claim 1 (a); harvesting "by centrifugation" (see middle of left column, p. 279) then said centrifuged "pellet (designated as the membrane fraction) was resuspended in buffer

AD (**500 mM NaCl**) with several strokes in a Potter homogenizer and recentrifuged" (see middle of left column, p. 279), which meets instant method steps of Claim 1(b) (c), wherein said homogenization process with a presence of the buffer AD (500mM NaCl) of any left over unbroken cells in the membrane fraction of Kempf et al. meets the instant method step of lysing cell. The method steps of Kemp et al. also teach "C12E9 (kept as a 2% aqueous stock solution) was added dropwise to a final concentration of 0.2%" (see middle of left column, p. 279), which meets the limitation of Claim 1(d). The P450 of Kempf et al. was recovered by the Ni^{2+} affinity column, which meets the limitation of Claim 1(e). According to the instant specification page 20, "the buffer comprising a salt which is readily soluble to provide a buffer having a conductivity of from 12 to 110 mS/cm" is "desirably a salt having a concentration in the 200-1000 mM range", "preferably the salt is a potassium or sodium salt of an anion" and "Potassium phosphate (KPi) is particularly preferred" (see page 20, Salt Buffer). Thus, the buffer AD of Kempf et al. with 500 mM NaCl have inherent conductivity within the range of 12 to 110 mS/cm. Thus, the method of Kempf et al. meets all limitations of Claims 1-3, 6-8, 10 and 22-23. According to the instant specification a salt concentration of 500 mM ± 50 mM would have 25-35 mS/cm (see page 20, lines 15-18); thus, the method steps of Kempf described above meet the limitation of Claim 21. Kempf et al. teach a method further comprising steps of the HTP hydroxylapatite purification of the P450. After the P450 bind to the hydroxylapatite column, the P450 was eluted with buffer H containing 200 mM NaPi and the "eluted material was dialyzed against buffer H". The elution step by Kemp et al. encompasses rinsing and removing the P450 steps of Claim 4 (e(ii)-(iii)).

The dialysis steps meets the limitation of Claim 4 reciting "rapidly desalting" in the Claim 4 (f) in view of broad and reasonable interpretation of the rapid desalting. Thus, the method steps of Kempf et al. meet all limitation of Claims 1-4, 6-8, 10 and 21-23.

Maintained-Claim Rejections - 35 USC § 103

18. The previous rejection of Claim 5 under 35 U.S.C. 103(a) as being unpatentable over Kempf et al. (1995, Archives of Biochemistry and Biophysics, vol. 321, p. 277-288, as cited in the IDS) in view of Anderson et al. (1968, Journal of Bacteriology, vol. 96, p 93-97) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the method of Kempf et al. does not anticipate the presently claimed invention and renders non obvious by Kempf et al. in combination with Anderson et al for the following resons. Applicants argue the P450 of Kempf et al. use 21% of detergent (see page 19, line 2, Remarks). However, Kempf et al. used "0.2%" as described above. Applicants argue (reciting multiple time throughout the Remarks) that the P450 of Kempf et al. is not suitable for crystallization. However, this is not the instant claim limitation. Applicants further argue the salt concentration of Kempf does not meet the instant claim limitation. The salt concentration of Kempf et al. meets the instant claim limitation as described in the 35 USC § 102 above. Applicants argue the method steps of Kempf et al. does not anticipate because the use of high salt (500 mM NaCl) by Kempf et al. is in different stages during the purification. As it is written, the instant claims does not exclude any additional method steps as long as those steps

includes the step recited in the instant claims in order in view of open-ended term "comprising" and the use of alphabet labeling each method step. Thus, as described above, the method of Kempf et al. meets all method steps of the instant claims in order and said method steps are within the scope of the instant claims.

Additionally, Applicants argue that "the inventors have discovered that by using a buffer with a high ionic strength in the initial cell lysis step it was possible to recover P450 without the need to recover a separate membrane fraction"; thus eliminate a step of recovery process and increase the overall yield of the protein, which is suitable for the production of crystals (see top of page 21, Remarks). However, for one skilled in the art, it has been known that high salt in the buffer would dissociate the membrane associating proteins (specially periplasmic membrane proteins) from the membrane part by general salting in or out process. One skilled in the art knows the overall purification steps are designed to balance between the factors comprising final yield and the purity according to characteristics of protein such as the stability. As long as the protein is stable, having additional separation step such as removing cytosolic part from the cell lysate would increase the purity of membrane associated protein since a purity of protein is considered as one of important factors in order to use it for a crystallization of protein, although not necessarily, because impure proteins have been crystallized in the past. The method of Kemp et al. seems to have "perceived need in the art to resuspend host cells expressing P450s in a buffer with low ionic strength" (as acknowledged by the Applicants' remarks, page 19, bottom) prior to the actual solublization of the P450 by high ionic salt of 500 mM NaCl for Ni^{2+} column chromatography in order to enhance the

overall purity by removing all the soluble proteins in the cytosol, wherein the purity of protein is one of important factor for setting up crystallization of a protein.

Applicants argue the cited Anderson et al. fails to address the deficiencies of Kempf et al. and request withdrawal of the instant 103 rejection.

As disclosed in the previous Office Action, Kempf et al. do not teach a method of purification of P450 comprising a step performing a size-exclusion chromatography to remove salt. Anderson et al. teach a method of isolating an enzyme using "gel filtration served simultaneously to desalt and fractionate the product" (see bottom of left column, p. 94).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice the method of Kempf et al. purifying N-terminal truncated human P450 2D6 and desalting the purified by using a method step performing size-exclusion chromatography of Anderson et al. instead of dialysis with a reasonable expectation of success to desalt P450 2D6 of Kempf et al. because size-exclusion column separates molecules by the size for the same purpose of dialysis by Kempf et al. The motivation to do so is provided by Anderson et al. who disclose "Gel filtration served simultaneously to desalt and fractionate the product" (see bottom of left column, p. 94). Thus, the gel filtration of Anderson et al. would be advantageous for the purification of a protein over the dialysis of Kempf et al. because, in addition to desalting the protein, gel filtration would provide simultaneous additional purification step. Therefore, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Maintained-Double Patenting

19. The previous provisional rejection of Claims 1-12 (and newly added Claims 21-23) on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/221,036 is maintained because of Applicants' request to hold the provisional obviousness-type double patenting rejection of Claim 1-12 until such time as allowable subject matter is identified.

Conclusion

20. Claims 1-13 and 21-23 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

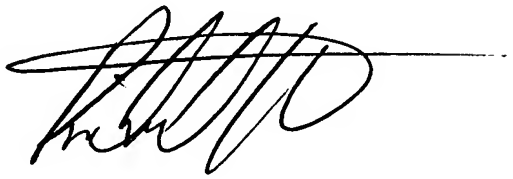
the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
August 27, 2007



RICHARD HUTSON, PH.D.
PRIMARY EXAMINER